

WHAT IS CLAIMED IS:

1. A process of producing agglomerates comprising the steps of:
  - (a) providing particles of at least one first material and particles  
5 of at least one solid binder, at least one of said first material and said solid binder having a preselected amount of convertible amorphous content which is capable of being converted to crystalline form upon exposure to a preselected stimulus, said convertible amorphous content being provided in an amount which is sufficient to allow for the formation of agglomerates;
  - 10 (b) agglomerating said particles of said first material and said solid binder while maintaining said preselected amount of convertible amorphous content; and thereafter
  - (c) exposing said convertible amorphous content within said agglomerates to said preselected stimulus so as to convert said convertible  
15 amorphous content to a crystalline form.
2. The process of claim 1 wherein said first material comprises a pharmacologically active agent.
- 20 3. The process of claim 2 wherein said pharmacologically active agent comprises at least one member selected from the group consisting of corticosteroids,  $\beta$ -agonists, anticholinergics, leukotriene antagonists and inhalable proteins or peptides.
- 25 4. The process of claim 2, wherein said pharmacologically active agent comprises at least one member selected from the group consisting of:  
mometasone furoate; beclomethasone dipropionate; budesonide; fluticasone;  
dexamethasone; flunisolide; triamcinolone; salbutamol; albuterol; terbutaline;  
salmeterol; bitolterol; ipratropium bromide; oxitropium bromide; sodium  
30 cromoglycate; nedocromil sodium; zafirlukast; pranlukast; formoterol;  
eformoterol; bambuterol; fenoterol; clenbuterol; procaterol; broxaterol; (22R)-

6 $\alpha$ , 9 $\alpha$ -difluoro-11 $\beta$ ,21-dihydroxy-16 $\alpha$ ,17 $\alpha$ -propylmethylenedioxy-4-pregnen-3,20-dione; TA-2005; tipredane; insulin; interferons; calcitonins; parathyroid hormones; and granulocyte colony-stimulating factor.

5            5.        The process of claim 2, wherein said pharmacologically active agent comprises mometasone furoate.

6.        The process of claim 2, wherein said particles of said pharmacologically active agent have an average particle size of 10  $\mu$ m or  
10   less.

7.        The process of claim 1, wherein said solid binder comprises at least one member selected from the group consisting of polyhydroxy aldehydes, polyhydroxy ketones, and amino acids.

15           8.        The process of claim 1, wherein said solid binder comprises a hydrated or anhydrous saccharide.

9.        The process of claim 1, wherein said solid binder comprises  
20   anhydrous lactose or a hydrated lactose.

10.       The process of claim 1 wherein said solid binder comprises anhydrous lactose.

25           11.       The process of claim 2, wherein said particles of said solid binder have an average particle size of 10  $\mu$ m or less.

12.       The process of claim 2, wherein said agglomerate contains between about 1% and about 50% convertible amorphous content.

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13. The process of claim 2, wherein said agglomerate contains between about 3% and about 30% convertible amorphous content.

14. The process of claim 2, wherein said agglomerate contains  
5 between about 5% and about 25% convertible amorphous content.

15. The process of claim 2, further comprising the step of mixing said particles of pharmacologically active agent and said solid binder prior to said agglomerating step.

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16. The process of claim 14, wherein said particles of pharmacologically active agent and said solid binder are mixed to substantial homogeneity.

17. The process of claim 2, wherein said particles of pharmacologically active agent and said solid binder are agglomerated in a pan rotated with an eccentric motion.

18. The process of claim 2, wherein said agglomerates have an  
20 average size of between about 300 and about 1000  $\mu\text{m}$ .

19. The process of claim 2, wherein said agglomerates have a range in size from between about 100 and about 1500  $\mu\text{m}$ .

20. The process of claim 1 wherein said preselected stimulus is atmospheric moisture.

21. The process of claim 1, wherein said solid binder is maintained at a moisture content of less than or equal to that of a relative humidity of  
30 25% when measured at 21°C, prior to crystallization.

22. The process of claim 1, wherein said solid binder is maintained at a moisture content of less than or equal to that of a relative humidity of 20% when measured at 21°C, prior to crystallization.

5           23. The process of claim 2, further comprising converting said convertible amorphous content of said agglomerate into a crystalline form by exposure of said agglomerates to an atmosphere having a moisture content equal to that of a relative humidity of between about 30% and about 80% when measured at 25°C.

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24. The process of claim 23, wherein said convertible amorphous content is converted into a crystalline form by exposure of said agglomerates to an atmosphere having a moisture content equal to that of a relative humidity of between about 40% and about 60% when measured at 25°C.

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25. The process of claim 2, wherein said particles of said agglomerate are more strongly bound to one another after conversion of said amorphous content to a crystalline form than before conversion.

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26. The process of claim 2, wherein said agglomerates have a crush strength of between about 50 mg and about 5,000 mg after conversion of said convertible amorphous content.

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27. The process of claim 2, wherein said agglomerates have a crush strength of between about 200 mg and about 1,500 mg after conversion of said convertible amorphous content.

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28. The process of claim 1, further comprising the step of micronizing said solid binder and/or said first material to impart thereto a preselected amount of amorphous content to the resulting particles prior to the step of providing said particles.

29. The process of claim 28, wherein said solid binder is micronized using jet milling with a substantially anhydrous gas.

5           30. The process of claim 2, wherein said pharmacologically active agent and said solid binder are mixed at a weight ratio of between about 1000:1 to 1:1000.

10           31. The process of claim 2, wherein said pharmacologically active agent and said solid binder are mixed at a weight ratio of between about 100:1 to 1:500.

15           32. The process of claim 2, wherein said pharmacologically active agent and said solid binder are mixed at a weight ratio of between about 100:1 to 1:300.

20           33. The process of claim 2, wherein said pharmacologically active agent and said solid binder are agglomerated at a weight ratio of between about 20:1 to about 1:20.

            34. The process of claim 2, wherein said pharmacologically active agent and said solid binder are agglomerated at a weight ratio of between about 1:3 to about 1:10.

25           35. The product of the process of claim 1.

            36. The product of the process of claim 2.

30           37. The product of the process of claim 3.

38. A process for producing agglomerates containing a pharmacologically active agent, comprising the steps of:

(a) providing at least one pharmacologically active agent having an average particle size of below about 10  $\mu\text{m}$ ;

5 (b) providing at least one solid binder having an average particle size of about 10  $\mu\text{m}$  or below; at least one of said pharmacologically active agent and said solid binder having a preselected amount of convertible amorphous content which is sufficient to allow for the formation of agglomerates upon conversion;

10 (c) forming a homogeneous mixture of said particles of said pharmacologically active agent and said solid binder while maintaining said preselected amount of convertible amorphous content;

(d) agglomerating said mixture of said particles of said pharmacologically active agent and said solid binder while maintaining said  
15 preselected amount of convertible amorphous content of said solid binder; and

(e) thereafter allowing said convertible amorphous content of said agglomerates to convert to a crystalline form; to form

(f) agglomerates which are free-flowing, have bridges and  
20 are characterized by having a strength of between 50 mg and 5000 mg.

39. The process of claim 38 wherein said pharmacologically active agent comprises at least one member selected from the group consisting of corticosteroids,  $\beta$ -agonists, anticholinergics, leukotriene antagonists and  
25 inhalable proteins or peptides.

40. The process of claim 38, wherein said pharmacologically active agent comprises mometasone furoate

30 41. The process of claim 38, wherein said solid binder comprises anhydrous lactose or a hydrated lactose.

42. The process of claim 38, wherein said agglomerate contains between about 1% and about 50% convertible amorphous content prior to conversion.

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43. The process of claim 38, wherein said agglomerate contains between about 3% and about 30% convertible amorphous content prior to conversion.

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44. The process of claim 38, wherein said agglomerate contains between about 5% and about 25% convertible amorphous content prior to conversion.

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45. The process of claim 38, wherein said agglomerates have a strength of between 200 mg and about 1500 mg.

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46. A dosage form of a pharmacologically active agent useful for administration by oral inhalation therapy consisting essentially of: agglomerates of particles of a pharmacologically active agent and particles of crystalline solid binder, said particles having an average particle size of 10  $\mu\text{m}$  or less and being provided in a weight ratio of between 100:1 to 1:500, said agglomerates having an average size of between 400 and 700  $\mu\text{m}$ , a bulk density of between about 0.2 and about 0.4  $\text{g/cm}^3$  and a crush strength of between 200 mg and about 1500 mg.

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47. The dosage form of claim 46, wherein said crystalline solid binder comprises lactose.

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48. The dosage form of claim 47, wherein said crystalline lactose comprises anhydrous lactose.

49. The dosage form of claim 46, wherein said agglomerates have a bulk density of between about 0.29 and about 0.38 g/cm<sup>3</sup>.

50. The dosage form of claim 46 wherein said pharmacologically  
5 active agent comprises at least one member selected from the group consisting of corticosteroids,  $\beta$ -agonists, anticholinergics, leukotriene antagonists and inhalable proteins or peptides.

51. The dosage form of claim 46, wherein said pharmacologically  
10 active agent comprises at least one member selected from the group consisting of: mometasone furoate; beclomethasone dipropionate; budesonide; fluticasone; dexamethasone; flunisolide; triamcinolone; salbutamol; albuterol; terbutaline; salmeterol; bitolterol; ipratropium bromide; oxitropium bromide; sodium cromoglycate; nedocromil sodium; zafirlukast;  
15 pranlukast; formoterol; eformoterol; bambuterol; fenoterol; clenbuterol; procaterol; broxaterol; (22R)-6 $\alpha$ , 9 $\alpha$ -difluoro-11 $\beta$ ,21-dihydroxy-16 $\alpha$ ,17 $\alpha$ -propylmethylenedioxy-4-pregnen-3,20-dione; TA-2005; tipredane; insulin; interferons; calcitonins; parathyroid hormones; and granulocyte colony-stimulating factor.

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52. The dosage form of claim 46 wherein said agglomerate includes no binder other than said solid binder.

53. An intermediate agglomerate useful for producing a free-flowing  
25 crystalline agglomerate dosage form of a pharmacologically active agent useful for administration by oral or nasal inhalation therapy, said intermediate agglomerates comprising: particles of said pharmacologically active agent and particles of solid binder, said pharmacologically active agent or said solid binder having a preselected amount of convertible amorphous content which  
30 is sufficient to allow for the formation of crystalline agglomerates upon exposure to moisture, said particles of said pharmacologically active agent



and said particles of said solid binder having an average particle size of 10  $\mu\text{m}$  or less, and said particles being provided in a weight ratio of between 1000:1 to 1:1000.

5            54.    The intermediate agglomerate of claim 53 having an average size of between 300 and 1000  $\mu\text{m}$ , and a bulk density of between about 0.2 and about 0.4  $\text{g}/\text{cm}^3$ .

10           55.    The intermediate agglomerate of claim 53, wherein said lactose comprises anhydrous lactose.

56.    The dosage form of claim 53, having a bulk density of between about 0.29 and about 0.38  $\text{g}/\text{cm}^3$ .

15           57.    The intermediate agglomerate of claim 53, having an average size of between 400 and about 700  $\mu\text{m}$ .

58.    The intermediate agglomerate of claim 53 wherein said pharmacologically active agent comprises at least one member selected from  
20    the group consisting of corticosteroids,  $\beta$ -agonists, anticholinergics, leukotriene antagonists and inhalable proteins or peptides.

59.    The intermediate agglomerate of claim 53, wherein said pharmacologically active agent comprises at least one member selected from  
25    the group consisting of: mometasone furoate; beclomethasone dipropionate; budesonide; fluticasone; dexamethasone; flunisolide; triamcinolone; salbutamol; albuterol; terbutaline; salmeterol; bitolterol; ipratropium bromide; oxitropium bromide; sodium cromoglycate; nedocromil sodium; zafirlukast; pranlukast; formoterol; eformoterol; bambuterol; fenoterol; clenbuterol;  
30    procaterol; broxaterol; (22R)-6 $\alpha$ , 9 $\alpha$ -difluoro-11 $\beta$ ,21-dihydroxy-16 $\alpha$ ,17 $\alpha$ -propylmethylenedioxy-4-pregnen-3,20-dione; TA-2005; tipredane; insulin;

interferons; calcitonins; parathyroid hormones; and granulocyte colony-stimulating factor.

5 60. The intermediate agglomerate of claim 63, having a convertible amorphous content of between about 1 and about 50% by weight.

10 61. A dosing system comprising: (a) an inhaler, said inhaler including a storage reservoir for storing an amount of a pharmacologically active agent in the form of a crystalline agglomerate, sufficient to provide a plurality of individual doses thereof, a metering device for measuring and metering a preselected amount of said pharmacologically active agent from said storage reservoir, and a nozzle for conveying said pharmacologically active agent from said metering device to the mouth or nose of a patient; and  
15 (b) an amount of a pharmacologically active agent sufficient to provide a plurality of individual doses thereof, said pharmacologically active agent being stored within said storage reservoir, being provided as an agglomerate of particles of said pharmacologically active agent and particles of a crystalline binder, wherein said particles have an average particle size of 10  $\mu\text{m}$  or less and the components thereof are provided in a weight ratio of between 1000:1  
20 to 1:1000, said agglomerates having an average size of between 300 and 1000  $\mu\text{m}$  and a bulk density of between about 0.2 and about 0.4  $\text{g}/\text{cm}^3$ ; and said agglomerate and said inhaler, when used in combination, being capable of producing a fine particle fraction of at least 10%, at an inhaled air flow rate about 60 L/min.

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62. The dosing system of claim 61, wherein said crystalline agglomerates have a strength of between about 50 mg and about 5000 mg and wherein said inhaler is designed such that it will impart to said agglomerated pharmacologically active agent an amount of force which is  
30 sufficient to produce a fine particle fraction of at least 10%, at an inhaled air flow rate about 60 L/min.

63. The dosing system of claim 61, wherein said crystalline agglomerates have a strength of between about 200 mg and about 1,500 mg and wherein said inhaler is designed such that it will impart to said
- 5 agglomerated pharmacologically active agent an amount of force which is sufficient to produce a fine particle fraction of at least 10%, at an inhaled air flow rate about 60 L/min.